

Pulmonary Arterial Hypertension in Children

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For the SSPH**

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Idiopathic or familial pulmonary arterial hypertension, congenital or acquired heart disease, persistent pulmonary hypertension of the newborn (PPHN) and neonatal lung disease are the most common causes of pulmonary hypertension in children. These etiologies are described in the revised classification of Venice (1).

Pulmonary arterial hypertension (PAH) remains a rare disease in childhood, associated with poor prognosis, if remained untreated. Twenty years ago, before the era of the new therapies, the reported median survival for children was 10 months, but data were obtained with a limited number of pediatric patients(2). Outcome seems to be worse in children as compared to adults. However, tremendous advances in the understanding of the pathogenesis of pulmonary vascular disease have been achieved during the last two decades. These advances have lead to the introduction of new therapies that have improved its prognosis even if a definite cure still is not possible.

Pathophysiology

Adult and pediatric PAH show some similarities but there are specificities for children. One must absolutely remember that pediatric patients are growing and this may play a role in the development of pulmonary vascular lesions. Pathobiology seems similar, but patients with congenital heart disease have a different way to reach advanced lesions. Although PPHN is classified in the group of pulmonary arterial hypertension (1), its natural history and its transient nature renders this etiology different from the other forms of PAH. Besides these considerations, the role of endothelial dysfunction and the abnormal balance of vasodilator-antimitotic versus vasoconstrictors-promitotic substances is also true for the pediatric population. We have now moved from the beliefs that PAH was a process driven by vasoconstriction only, to a disease characterized by proliferation and remodeling. Other potential causes are currently studied such as

serotonin transporters and potassium channels anomalies. A genetic mutation of BMPR2 has been recognized in some patients with familial (> 50% of the patients) and idiopathic (~20-25%) PAH (3). Genetics in the pediatric population is still not clear but BMPR2 seems also involved in some patients. The BMPR2 is part of the TGF beta superfamily and is thought to be involved in the apoptosis/proliferation process. Studies available so far are not consistent but it appears that BMPR2 mutations also play a role in pediatric PAH.

Diagnosis

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure of more than 25 mmHg at rest or more than 30 mmHg during exercise, but usually pulmonary pressures are considerably higher in children. A classification for pulmonary hypertension has been proposed at the last world meeting for pulmonary hypertension held in Venice in 2003(1). The Venice classification groups pathologies mainly in relation to their therapeutic approach. This could help to perform studies with similar or at least homogenous group of patients and thus better assess the efficacy of the new therapies. Even if not perfect for pediatric patients, this classification is of help and includes most of the diagnosis encountered in our young population.

Symptoms in children are frequently misleading to diagnosis like asthma or epilepsy for months before reaching the diagnosis of PAH. As in adults, a high degree of suspicion should be the rule. Children should undergo a similar diagnostic approach as the one described in adults(4). Chest radiography, electrocardiogram and echocardiography should be performed as a first line as well as arterial blood gases, oxygen saturation, pulmonary function tests and exercise testing. Ventilation perfusion scan, chest CT and abdominal ultrasound should be performed to define potential etiologies. Similarly, serological studies and blood screening for connective tissue

diseases, HIV testing, and coagulation studies may help to discover potential causes of pulmonary hypertension.

Finally, pulmonary hypertension must be confirmed by catheterization and pulmonary vasoreactivity testing performed during this study. The acute testing should be performed following the adult recommendations preferably with inhaled NO or IV epoprostenol or adenosine. Inhaled iloprost may also be used, even though dosage remains poorly defined in children. The vasoreactivity testing is of major importance. According to the new definition, responders should display a decrease of $> 10\text{mmHg}$ with a mean pulmonary arterial pressure of $< 40\text{mmHg}$ and a normal or increased cardiac output. True responders can be treated successfully with calcium channel blockers with success. Based on this definition only 6 to 8 % of adult patients with PAH are considered as responders(5). Whereas this approach is applicable to pediatric patients is still a matter of debate between specialists. Data are controversial regarding the percentage of responders in children; Numbers varying between 6 to 8%, as in adults, up to 40%.

Treatments

Conventional therapy for PAH in children, either of idiopathic origin or with associated risk factors, includes actually, beyond the neonatal period, the association of warfarin, digitalis, diuretics and supplemental oxygen when required. The use of anticoagulants is advocated even if no studies have been performed in children showing the same beneficial effect as in adults. The use of digoxin remains controversial in respect to its effect on the right ventricle. Treatments, particularly new therapies, for other forms of pulmonary hypertension are less defined and not discussed in this brief review.

Calcium channel blockers are still indicated in responders as previously described. Most studies have used high doses of but indeed the optimal dose is not clearly defined.

Long-acting nifedipine 120-240 mg daily or amlodipine 20-40 mg daily are the suggested doses both in adults and children, children tolerating and appearing to need a higher mg/kg than adults but optimal doses remain uncertain. Serial evaluation is of major importance to evaluate continuous efficacy.

For other therapies, recommendations are unfortunately based on the adult experience and thus follow the algorithm developed during the Venice meeting in 2003 and further from the ESC guidelines published in 2004(6). This algorithm is regularly adapted with regards to the new studies and developments.

The current therapeutic approach includes also the use of prostanoids, agents in the nitric oxide pathway, phosphodiesterase 5 inhibitors, and endothelin-1 receptor antagonists.

Prostanoids

Long-term continuous infusion of prostacyclin (epoprostenol) has been shown to improve physical capacity and reduce mortality in PAH both in adults and in children(7, 8). The doses are similar as in adults starting at 2ng/kg/min with incremental increases to obtain a significant beneficial effect without side effects. It has been reported in adults that daily repetitive inhalation of iloprost, a prostacyclin analogue, is suitable for long-term therapy of pulmonary hypertension(9); such a beneficial effect can be obtained in the paediatric population as well. Other potential therapies include: oral (beraprost) or subcutaneous (treprostinil) administration of prostacyclin. However, beraprost has failed to demonstrate long-term efficacy in adults. This treatment is used in Japan where it was approved long time ago but is not currently approved in Europe and in the USA. Subcutaneous treprostinil is approved for adult therapy(10) but shows a major drawback in children because of the pain at the site of

injection. This molecule has been approved recently for the IV administration in the US and is also studied as a potential inhaled therapy in adults.

Nitric oxide pathway/phosphodiesterase 5 inhibitor (Sildenafil)

Chronic treatment with inhaled nitric oxide is currently not available. There is a major interest in the phosphodiesterase 5 inhibitor, sildenafil. SUPER 1, an adult randomized placebo controlled study, has shown recently that sildenafil improves exercise capacity in class II/III PAH patients(11); Several case reports or uncontrolled studies have shown efficacy in the pediatric population as well(12). Preliminary safety and efficacy trials are currently conducted with sildenafil. Sildenafil has recently been approved by the FDA and the EMEA at a dose of 20 mg tid in adults.

Endothelin receptor antagonists

So far there are only data in children with the dual endothelin receptor antagonist bosentan(13, 14). Data with sitaxsentan and ambrisentan, both specific ET_A receptor antagonists, are so far only available in adults. Preliminary reports with bosentan in children are encouraging. However, randomized controlled trials, such as those recently performed in adults, are not available. Non-controlled studies seem to show the same results as those obtained in the adult population. At present suggested dosage for children is based on a pharmacokinetic study(13). Currently another pharmacokinetic study is conducted with the aim to develop a pediatric formulation of bosentan.

Combined therapies

Combined approaches (iloprost+sildenafil, iloprost+bosentan or bosentan+sildenafil) may further improve the efficacy of these new therapies. However, the first reports of these combinations have been presented only recently in adults and there are only few case reports in the pediatric population.

Interventional therapies

Finally, interventional therapy includes lung transplantation, which is the only curative therapy, but shortage of donors remains a problem. Atrioseptostomy to decompress the right atrium may offer a possible palliation; it has been shown to prolong survival and improve symptoms in patients with refractory right heart failure(15). Recently, the creation of a Potts shunt has also shown encouraging results(16).

Therapeutic advances over the past decades have improved the prognosis of PAH in children. Early diagnosis and referral to specialized centers is of utmost importance. Several new therapies are available but the number of pediatric patients enrolled in randomized trials is very small and does not allow for evidenced based therapeutical decisions; therefore careful attention should be observed to perform studies that deliver significant and useful information as how to treat these precarious patients. Serial evaluation is of utmost importance to assess the efficacy of therapies and regular adjustments are necessary to obtain beneficial results. So far we may use the recent adult therapeutical algorithm of the Columbia group (figure 1) with some adaptations. However this approach requires continuous refinements based on new studies and authorities approval.

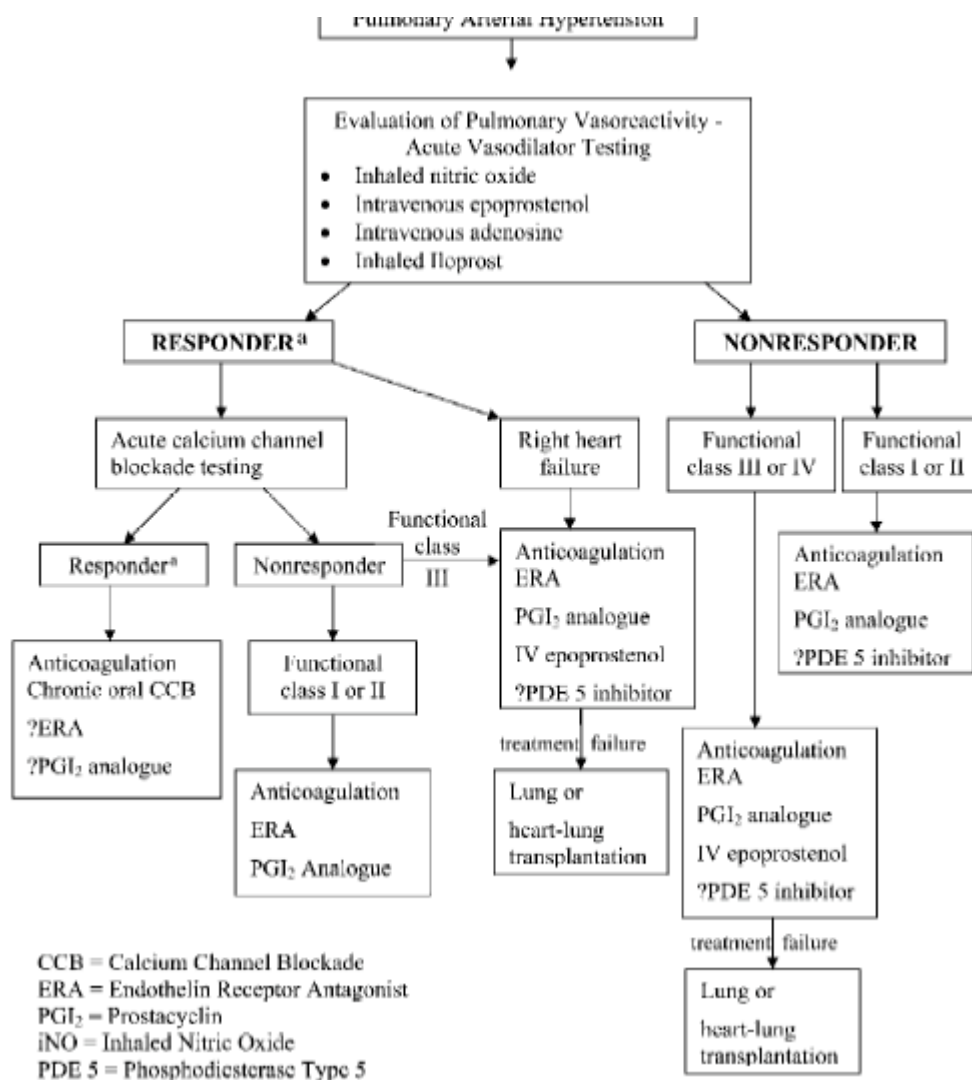


Figure 1: Treatment guidelines for pediatric pulmonary arterial hypertension (PAH). A, Treatment strategies for children with idiopathic PAH. Reproduced from Rosenzweig EB, Barst RJ. Idiopathic pulmonary arterial hypertension in children. *Curr Opin Pediatr* 2005;17:372-80.

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